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Complete Summary

GUIDELINE TITLE

Practice parameter: Anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology.

BIBLIOGRAPHIC SOURCE(S)

Glantz MJ, Cole BF, Forsyth PA, Recht LD, Wen PY, Chamberlain MC, Grossman SA, Cairncross JG. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000 May 23;54(10):1886-93. [85 references]

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SCOPE

DISEASE/CONDITION(S)

Seizures (convulsions) associated with primary or metastatic brain tumors (brain neoplasms)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Prevention
Risk Assessment

CLINICAL SPECIALTY

Internal Medicine
Neurological Surgery
Neurology

Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To review the evidence on the administration of prophylactic anticonvulsants to patients with brain tumors and to provide specific recommendations based on the analysis of the evidence

TARGET POPULATION

Patients with newly diagnosed brain tumors (primary or metastatic)

INTERVENTIONS AND PRACTICES CONSIDERED

Prophylactic use of anticonvulsant medications (e.g., phenytoin [Dilantin], carbamazepine, phenobarbital, and valproic acid [Depakote]) in patients with primary or metastatic brain tumors.

MAJOR OUTCOMES CONSIDERED

- Seizure-free survival (time to first seizure or death, whichever occurred first)
- Overall survival

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Pertinent studies were identified through MEDLINE searches of the years 1966 to July 1999 using the search parameters SEIZURE (exp), BRAIN NEOPLASMS (exp), ANTICONVULSANTS (exp), CRANIOTOMY (exp), and PRIMARY PREVENTION (exp). All 829 articles identified in this way were reviewed, and all studies, including randomized clinical trials, cohort studies, and case series, that considered the prophylactic use of anticonvulsants in patients with brain tumors were selected. The reference list of each of the selected papers was reviewed for additional pertinent studies. CANCERLIT and the Cochrane Database were also queried. Lastly, all abstracts indexed under "seizure," "brain tumor," or "anticonvulsant," which appeared in the American Society of Clinical Oncology, American Academy of Neurology, American Neurologic Association, American Epilepsy Society, and American Association of Neurologic Surgeons abstract books between the years

1982 and 1999, were reviewed. When overlapping data were published more than once (for example, as a preliminary communication and subsequently, with additional patients, in final form) only the most updated version was selected. Two studies addressed the issue of prophylactic anticonvulsant use in patients with a variety of neurologic conditions, including patients with brain tumors, but neither the published data nor queries to the authors ultimately allowed separation of patients with brain tumors from those with other diagnoses. In a third study, prophylactic anticonvulsant medication was administered, and follow-up was carried out for only 3 postoperative days. These studies were excluded.

NUMBER OF SOURCE DOCUMENTS

829 source documents

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Ratings for the Quality of the Evidence:

Class I. Must have all of a through d. (a) Prospective study of a well-defined cohort which includes a description of the nature of the population, the inclusion/exclusion criteria, demographic characteristics such as age and sex, and seizure type. (b) The sample size must be adequate with enough statistical power to justify a conclusion or for identification of subgroups for whom testing does or does not yield significant information. (c) The interpretation of evaluations performed must be done blinded to outcome. (d) There must be a satisfactory description of the technology used for evaluations (e.g., electroencephalogram, magnetic resonance imaging).

Class II. Must have a or b. (a) Retrospective study of a well-defined cohort which otherwise meets criteria for class 1a, b and 1d. (b) Prospective or retrospective study which lacks any of the following: adequate sample size, adequate methodology, a description of inclusion/exclusion criteria, and information such as age, sex and characteristics of the seizure.

Class III. Must have a or b. (a) A small cohort or case report. (b) Relevant expert opinion, consensus, or survey. A cost-benefit analysis or a meta-analysis may be class I, II, or III, depending on the strength of the data upon which the analysis is based.

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Observational Trials
Meta-Analysis of Randomized Controlled Trials

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

A meta-analysis was conducted on seizure incidence using all identified prospective, randomized clinical trials. Seizure-free survival (time to first seizure or death, whichever occurred first) and overall survival (time to death) were also calculated for the two studies from which patient-level data were available.

For each end point in each trial, an odds ratio, comparing the odds of the event in the anticonvulsant prophylaxis group relative to the control group, was computed. The trial-specific odds ratios were then averaged to provide a meta-analysis summary. The meta-analysis odds ratio was used subsequently to test whether anticonvulsant prophylaxis affected the odds of an event. All statistical tests were performed using a Z test. Two-sided p values were used to compare the treatment groups with respect to the odds of an event. A p value less than 0.05 was considered significant.

For each clinical trial used in the seizure incidence analysis, the odds ratio describing the odds of seizure in the anticonvulsant group relative to the control group was computed along with the variance (V) of log(odds ratio), and a 95% confidence interval for the odds ratio estimate. These computations were performed using standard techniques. The meta-analysis odds ratio was then obtained by computing the weighted average of the log(odds ratio) estimates, for which the weightings were defined by the inverse variance (1/V) of log(odds ratio) for each trial. In this way, each trial was weighted inversely according to the amount of variation associated with the log(odds ratio) estimate. The standard error of the weighted average was obtained by dividing the sum of the â œexponentiatedâ to obtain the overall summary odds ratio. Statistical inference was carried out on the log(odds ratio) scale using normal (Z) distribution theory.

The meta-analysis of seizure-free survival was performed using previously established techniques. For each clinical trial the Kaplan–Meier method was used to estimate seizure-free survival according to treatment group. The treatment comparison was then made using the logrank test, which evaluates the observed number of events (seizure or death) on each study arm compared with the number of events that would be expected to occur if each treatment group had the same risk. The logrank analyses were then averaged to obtain a meta-analysis comparison of the treatment groups in terms of an odds ratio. The meta-analysis of overall survival was conducted in a similar fashion.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Definitions for the Strength of the Recommendations:

Standard. A principle for patient management that reflects a high degree of clinical certainty (usually requires one or more Class I studies that directly address the clinical question, or overwhelming Class II evidence when circumstances preclude randomized clinical trials).

Guideline. A recommendation for patient management that reflects moderate clinical certainty (usually requires one or more Class II studies or a strong consensus of Class III evidence).

Practice Option. Strategy for patient management for which clinical utility is uncertain (inconclusive or conflicting evidence or opinion).

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Excerpted by the National Guideline Clearinghouse (NGC)

Each clinical recommendation is rated based on the strength of the evidence. Definitions of the strength of the recommendations (standard, guideline, practice option) and quality of the evidence (Class I-Class III) are presented at the end of the Major Recommendations field.

Summary

Twelve studies have examined, either in randomized controlled trials or cohort studies, the ability of prophylactic anticonvulsants to prevent first seizures in patients with brain tumors, and none have demonstrated efficacy. Four of these studies provide level I evidence. A meta-analysis of these four studies also revealed no evidence of an effect on the frequency of first seizures in patients receiving anticonvulsant prophylaxis. In contrast, deleterious interactions with cytotoxic drugs and corticosteroids are a major concern, and the incidence and severity of anticonvulsant side effects appear to be appreciably higher (20 to 40%) in brain tumor patients than in the general population of patients receiving anticonvulsants. This increased incidence is due at least in part to the additive or synergistic effects of concurrently administered drugs (especially chemotherapeutic agents) and to the underlying brain tumor.

Conclusions

Seizures are a common and sometimes devastating complication of brain tumors, and meticulous attention to their diagnosis and treatment is critical. The available evidence suggests, however, that prophylactic administration of anticonvulsant medications does not provide substantial benefit (i.e., a risk reduction of 26% or more for seizure-free survival), whereas anticonvulsant-associated side effects are especially common and occasionally life-threatening.

Many patients who experienced seizures while receiving anticonvulsant prophylaxis had subtherapeutic anticonvulsant blood levels. Although this may provide one explanation for the ineffectiveness of anticonvulsant prophylaxis in some patients, it did not change the conclusions of the one randomized controlled trial that addressed that issue specifically. In that study, 23% of patients receiving anticonvulsant prophylaxis who experienced a seizure had subtherapeutic levels. Reanalysis excluding patients with subtherapeutic levels still showed no benefit for anticonvulsant prophylaxis. Moreover, even in the setting of scrupulously monitored prospective studies in epileptic patients, subtherapeutic levels are extremely common, partly because of drug interactions. Rather than change the implications of these studies, this high rate of subtherapeutic levels simply reflects a clinical reality.

Clinical Recommendations

1. In patients with newly diagnosed brain tumors, anticonvulsant medications are not effective in preventing first seizures. Because of their lack of efficacy and their potential side effects, prophylactic anticonvulsants should not be used routinely in patients with newly diagnosed brain tumors (Standard).
2. In patients with brain tumors who have not had a seizure, tapering and discontinuing anticonvulsants after the first postoperative week is appropriate, particularly in those patients who are medically stable and who are experiencing anticonvulsant-related side effects (Guideline).

Definitions:

Strength of the Recommendations:

Standard. A principle for patient management that reflects a high degree of clinical certainty (usually requires one or more Class I studies that directly address the clinical question, or overwhelming Class II evidence when circumstances preclude randomized clinical trials).

Guideline. A recommendation for patient management that reflects moderate clinical certainty (usually requires one or more Class II studies or a strong consensus of Class III evidence).

Practice Option. Strategy for patient management for which clinical utility is uncertain (inconclusive or conflicting evidence or opinion).

Quality of the Evidence:

Class I. Must have all of a through d. (a) Prospective study of a well-defined cohort which includes a description of the nature of the population, the

inclusion/exclusion criteria, demographic characteristics such as age and sex, and seizure type. (b) The sample size must be adequate with enough statistical power to justify a conclusion or for identification of subgroups for whom testing does or does not yield significant information. (c) The interpretation of evaluations performed must be done blinded to outcome. (d) There must be a satisfactory description of the technology used for evaluations (e.g., electroencephalogram, magnetic resonance imaging).

Class II. Must have a or b. (a) Retrospective study of a well-defined cohort which otherwise meets criteria for class 1a, b and 1d. (b) Prospective or retrospective study which lacks any of the following: adequate sample size, adequate methodology, a description of inclusion/exclusion criteria, and information such as age, sex and characteristics of the seizure.

Class III. Must have a or b. (a) A small cohort or case report. (b) Relevant expert opinion, consensus, or survey. A cost-benefit analysis or a meta-analysis may be class I, II, or III, depending on the strength of the data upon which the analysis is based.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Twelve studies were identified that provided data on the frequency of first seizures in patients with brain tumors relative to the treatment of interest (prophylactic anticonvulsant use versus no prophylactic anticonvulsants). Of these, four were randomized clinical trials that provided level I evidence, and eight were cohort studies that provided level II evidence (see the "Major Recommendations" section for a description of the levels of evidence).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Reduction in the incidence of anticonvulsant-associated side effects, which are occasionally life-threatening, in patients with brain tumors who are not experiencing seizures
- Reduction in the incidence of anticonvulsant drug interactions with chemotherapeutic agents and steroids in patients with brain tumors

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The American Academy of Neurology recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.
- The meta-analysis technique itself is not infallible. Its value depends on the quality of its component studies. A meta-analysis cannot evaluate or correct for bias in its component studies, and can provide misleading results if the component studies are very heterogeneous with respect to patient characteristics, the disease studied, or the intervention. The studies included in the current meta-analysis were all prospective, randomized, and controlled; the most effective strategy for minimizing the risk of bias and confounding. As described in the sections titled "Description of Process" and "Results" in the original guideline document, and as summarized in Table 2 titled "Anticonvulsant Prophylaxis Studies in Patients with Brain Tumors" (see the original guideline document), the studies were evaluated specifically to ensure good patient homogeneity. For these reasons, this meta-analysis does provide a reliable estimate of the overall lack of effect of anticonvulsant prophylaxis in patients with brain tumors.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Safety

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000 May

GUIDELINE DEVELOPER(S)

American Academy of Neurology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Academy of Neurology (AAN)

GUIDELINE COMMITTEE

Quality Standards Subcommittee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Subcommittee Members: Gary Franklin, MD, MPH (Co-Chair); Catherine Zahn, MD (Co-Chair); Milton Alter, MD, PhD; Stephen Ashwal, MD; John Calverley, MD; Richard Dubinsky, MD; Jacqueline French, MD (facilitator); Michael Greenberg, MD; Gary Gronseth, MD; Deborah Hirtz, MD; Robert Miller, MD; and James Stevens, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the AAN Web site.

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

AVAILABILITY OF COMPANION DOCUMENTS

- Practice statement definitions. St. Paul (MN): American Academy of Neurology.
- Practice statement development. St. Paul (MN): American Academy of Neurology.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on November 4, 2001. The information was verified by the guideline developer as of December 20, 2001.

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